

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
3 October 2002 (03.10.2002)

PCT

(10) International Publication Number
WO 02/076949 A1

(51) International Patent Classification⁷: **C07D 231/06**, (74) Agent: **MUIS, Maarten; OCTROOIBUREAU ZOAN B.V., P.O. Box 140, NL-1380 AC Weesp (NL).**
401/04, A61K 31/415, A61P 25/00

(21) International Application Number: **PCT/EP02/03079**

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(22) International Filing Date: 18 March 2002 (18.03.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
01201062.5 22 March 2001 (22.03.2001) EP

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (*for all designated States except US*): **SOLVAY PHARMACEUTICALS B.V. [NL/NL]; C.J. Van Houtenlaan 36, NL-1381 CP Weesp (NL).**

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



A1

WO 02/076949

(54) Title: **4,5-DIHYDRO-1H-PYRAZOLE DERIVATIVES HAVING CB₁-ANTAGONISTIC ACTIVITY**

(57) **Abstract:** The present invention relates to a group of novel 4,5-dihydro-1H-pyrazole derivatives having S configuration at the 4-position of their 4,5-dihydro pyrazole ring which are potent antagonists of the cannabis CB₁-receptor. The compounds have the general formula (I) wherein R and R₁ are the same or different and represent 3-pyridyl or 4-pyridyl or phenyl which may be substituted with halogen or methoxy, -R₂ and R₃ are the same or different and represent hydrogen, alkyl (1-3 C) or dimethylamino- R₄ represents phenyl which may be substituted with 1 or 2 substituents selected from the group halogen atoms, trifluoromethyl, methoxy and alkyl (1-3 C) and tautomers, prodrugs and salts thereof. These enantiomers are much more potent and selective antagonists of the cannabis CB₁-receptor, than the other enantiomer.

4,5-Dihydro-1H-pyrazole derivatives having CB₁-antagonistic activity

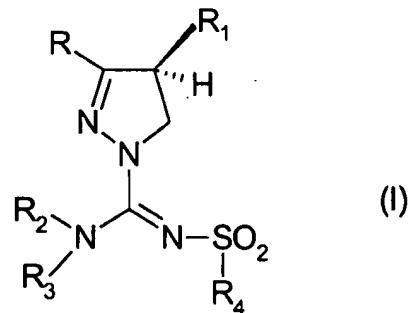
5 The present invention relates to a group of novel enantiomers of 4,5-dihydro-1H-pyrazole derivatives having S configuration at the 4-position of their 4,5-dihydropyrazole ring, to methods for the preparation of these compounds, and to pharmaceutical compositions containing one or more of these compounds as an active component.

10 The above mentioned (4S)-4,5-dihydro-1H-pyrazoles are potent Cannabis-1 (CB₁) receptor antagonists with utility for the treatment of psychiatric and neurological disorders.

15 Cannabinoids are present in the Indian hemp *Cannabis Sativa L.* and have been used as medicinal agents for centuries (Mechoulam, R.; Feigenbaum, J.J. *Prog. Med. Chem.* 1987, 24, 159). However, only within the past ten years the research in the cannabinoid area has revealed pivotal information on cannabinoid receptors and their (endogenous) agonists and antagonists. The discovery and the subsequent cloning of two different subtypes of Cannabinoid receptors (CB₁ and CB₂) stimulated the search for novel cannabinoid receptor antagonists (Munro, S.; Thomas, K.L.; Abu-Shaar, M. *Nature* 1993, 365, 61. Matsuda, L.A.; Bonner, T.I. *Cannabinoid Receptors*, Pertwee, R.G. Ed. 1995, 117, Academic Press, London). In addition, pharmaceutical companies became interested in the development of cannabinoid drugs for the treatment of diseases connected with disorders of the cannabinoid system. The wide distribution of CB₁ receptors in the brain, in combination with the strictly peripheral localisation of the CB₂ receptor, makes the CB₁ receptor a very interesting molecular target for CNS-directed drug discovery in the areas of both psychiatric and neurological disorders (Consroe, P. *Neurobiology of Disease* 1998, 5, 534. Pop, E. *Curr. Opin. In CPNS Investigational Drugs* 1999, 1, 587. Greenberg, D.A. *Drug News Perspect.* 1999, 12, 458). Hitherto, three types of distinct CB₁ receptor antagonists are known. Sanofi disclosed their diarylpyrazole congeners as selective CB₁ receptor antagonists. A representative example is SR-141716A, which is currently undergoing Phase II clinical development for psychotic disorders (Dutta, A.K.; Sard, H.; Ryan, W.; Razdan, R.K.; Compton, D.R.; Martin, B.R. *Med. Chem. Res.* 1994, 5, 54. Lan, R.; Liu, Q.; Fan, P.; Lin, S.; Fernando, S.R.; McCallion, D.; Pertwee, R.; Makriyannis, A. *J. Med. Chem.* 1999, 42, 769. Nakamura-Palacios, E.M.; Moerschbaecher, J.M.; Barker, L.A. *CNS Drug Rev.* 1999, 5, 43). Aminoalkylindoles have been disclosed as CB₁ receptor antagonists. A representative example is Iodoprvadoline (AM-630), which was introduced in

1995. AM-630 is a CB₁ receptor antagonist, but sometimes behaves as a weak partial agonist (Hosohata, K.; Quock, R.M.; Hosohata, Y.; Burkey, T.H.; Makriyannis, A.; Consroe, P.; Roeske, W.R.; Yamamura, H.I. *Life Sc.* **1997**, *61*, PL115). More recently, researchers from Eli Lilly described aryl-aryl substituted benzofurans as selective CB₁ receptor antagonists (e.g. LY-320135) (Felder, C.C.; Joyce, K.E.; Briley, E.J.; Glass, M.; Mackie, K.P.; Fahey, K.J.; Cullinan, G.J.; Hunden, D.C.; Johnson, D.W.; Chaney, M.O.; Koppel, G.A.; Brownstein, M. J. *Pharmacol. Exp. Ther.* **1998**, *284*, 291). Recently, 3-alkyl-5,5'-diphenylimidazolidinediones were described as cannabinoid receptor ligands, which were indicated to be cannabinoid antagonists (Kanyonyo, M.; Govaerts, S.J.; Hermans, E.; Poupaert, J.H., Lambert, D.M. *Biorg. Med. Chem. Lett.* **1999**, *9*, 2233). Interestingly, many CB₁ receptor antagonists have been reported to behave as inverse agonists *in vitro* (Landsman, R.S.; Burkey, T.H.; Consroe, P.; Roeske, W.R.; Yamamura, H.I. *Eur. J. Pharmacol.* **1997**, *334*, R1). Recent reviews provide a nice overview of the current status in the cannabinoid research area (Mechoulam, R.; Hanus, L.; Fride, E. *Prog. Med. Chem.* **1998**, *35*, 199. Lambert, D.M. *Curr. Med. Chem.* **1999**, *6*, 635. Mechoulam, R.; Fride, E.; Di Marzo, V. *Eur. J. Pharmacol.* **1998**, *359*, 1).

20 It has now surprisingly been found that the novel enantiomers of 4,5-dihydro-1H-pyrazole derivatives having S configuration at the 4-position of their 4,5-dihydro pyrazole ring of the formula (I), prodrugs thereof, tautomers thereof and salts thereof



25 wherein

- R and R₁ are the same or different and represent 3-pyridyl or 4-pyridyl, or phenyl which may be substituted with halogen or methoxy,
- R₂ and R₃ are the same or different and represent hydrogen, alkyl (1-3 C) or dimethylamino
- R₄ represents phenyl which may be substituted with 1, 2 or 3 substituents selected from the group halogen, trifluoromethyl, methoxy and alkyl (1-3 C)

are much more potent and selective antagonists of the cannabis CB₁-receptor, than the correspondence R-enantiomer.

5 Due to the potent CB₁ antagonistic activity the compounds according to the invention are suitable for use in the treatment of psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders and appetite disorders, obesity, neurological disorders such as dementia, dystonia, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, as well as for the treatment of pain disorders and other CNS-diseases involving cannabinoid neurotransmission, and in the treatment of gastrointestinal disorders and cardiovascular disorders.
10

15 The affinity of the compounds of the invention for cannabinoid CB₁ receptors was determined using membrane preparations of Chinese hamster ovary (CHO) cells in which the human cannabis CB₁ receptor is stably transfected in conjunction with [3H]CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the [3H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand was performed by filtration
20 over glassfiber filters. Radioactivity on the filter was measured by liquid scintillation counting.

25 The cannabinoid CB₁ antagonistic activity of compounds of the invention was determined by functional studies using CHO cells in which human cannabinoid CB₁ receptors are stably expressed. Adenylyl cyclase was stimulated using forskolin and measured by quantifying the amount of accumulated cyclic AMP. Concomitant activation of CB₁ receptors by CB₁ receptor agonists (e.g. CP-55,940 or (R)-WIN-55,212-2) can attenuate the forskolin-induced accumulation of cAMP
30 in a concentration-dependent manner. This CB₁ receptor-mediated response can be antagonised by CB₁ receptor antagonists such as the compounds of the invention.

35 The invention relates both to the E isomer, Z isomer and E/Z mixtures of compounds having formula (I).

The compounds can be brought into forms suitable for administration by means of usual processes using auxiliary substances and/or liquid or solid carrier materials.

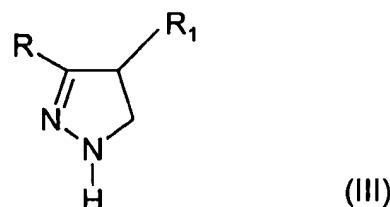
The compounds of the invention having formula (III) (*vide infra*) can be obtained according to methods known, for example: a) EP 0021506; b) DE 2529689.

A suitable synthesis for the racemic compounds according to the present
5 invention is the following:

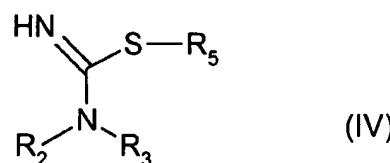
Synthesis route A

Step 1 of route A

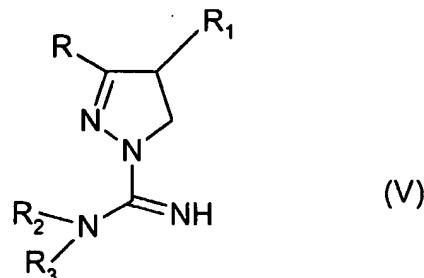
10 Reaction of a compound having formula (III)



with a compound having formula (IV)



15 wherein R₅ represents a lower alkyl group, such as for example 2-methyl-2-thiopseudourea, or with a suitable salt form thereof in the presence of a base. This reaction gives a 4,5-dihydro-1H-pyrazole-1-carboxamidine derivative having formula (V)



20 wherein the symbols have the meanings as mentioned above. Compounds having formula (V) wherein R, R₁, R₂ and R₃ have the meaning as described herein above for compound (I) are new.

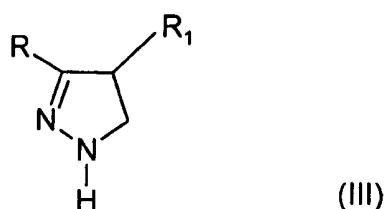
Alternatively, a compound having formula (III) is reacted with a so-called guanylating agent. Examples of such guanylating agents are 1H-pyrazole-1-carboxamidine and its salts (for example the hydrochloride salt) and 3,5-dimethyl-
5
1H-pyrazole-1-carboxamidine and its salts (for example the nitrate salt) and the like. This reaction gives a carboxamidine derivative having formula (V).

Alternatively, a compound having formula (III) is reacted with a so-called protected guanylating agent. Examples of such protected guanylating agents are N-(benzyloxycarbonyl)-1H-pyrazole-1-carboxamidine, N-(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamidine and N,N'-bis-(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamidine and the like. This reaction gives after deprotection a compound having formula (V).
10
15

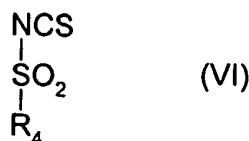
Step 2 of route A
The compound having formula (V) is reacted with an optionally substituted compound of the formula R₄-SO₂X, wherein R₄ has the above mentioned meaning and X represents a halogen atom. This reaction is preferably carried out in the presence of a base, such as triethylamine in an aprotic solvent, such as
20
acetonitrile.

Synthesis route A1

Step 1 of route A1
25 Reaction of a compound having formula (III)

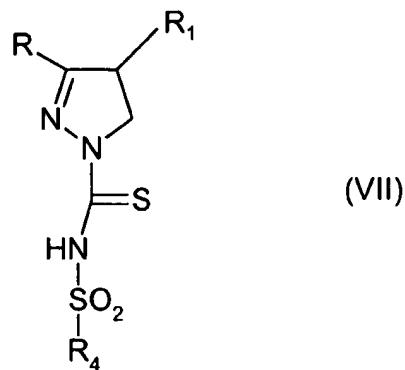


with a thioisocyanate derivative having formula (VI) .



This reaction is preferably carried out in an inert organic solvent, such as for example acetonitrile.

This reaction gives a thiocarboxamide derivative having formula (VII). Compounds having formula (VII) wherein R, R₁ and R₄ have the meaning as described herein above for compound (I) are new.



5

Step 2 of route A1

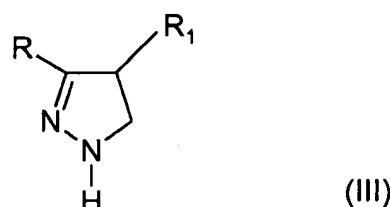
Reaction of a compound having formula (VII) with an amine in the presence of a mercury(II) salt, such as for example HgCl₂, gives a compound having formula (I). This reaction is preferably carried out in a polar organic solvent, such as for example acetonitrile.

10

Synthesis route A2

Step 1 of route A2

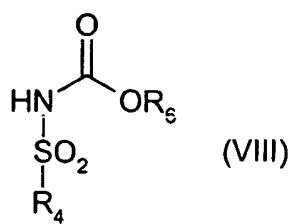
Reaction of a compound having formula III



15

with a carbamate ester derivative having formula (VIII).

7

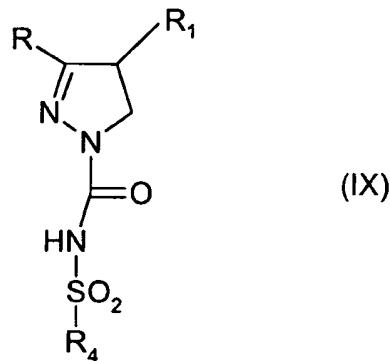


(VIII)

wherein R_6 represents a lower alkyl group, for example methyl.

This reaction is preferably carried out in an inert organic solvent, such as for example 1,4-dioxane.

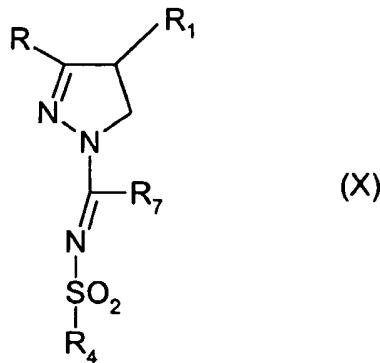
5 This reaction gives a 4,5-dihdropyrazole-1-carboxamide derivative having formula (IX). Compounds having formula (IX) wherein R , R_1 and R_4 have the meaning as described herein above for compound (I) are new.



(IX)

Step 2 of route A2

10 Reaction of a compound having formula (IX) with a halogenating agent, such as for example PCl_5 , gives a 4,5-dihdropyrazole-1-carboximidoyl halogenide derivative having formula (X).



wherein R₇ represents a halogen atom, such as for example chloro. This reaction is preferably carried out in an inert organic solvent, such as for example chlorobenzene.

5 Compounds having formula (X) wherein R, R₁ and R₄ have the meaning as described herein above for compound (I) and wherein R₇ represents a halogen atom are new.

Step 3 of route A2

10 Reaction of a compound having formula (X) with an amine gives a compound having formula (I).

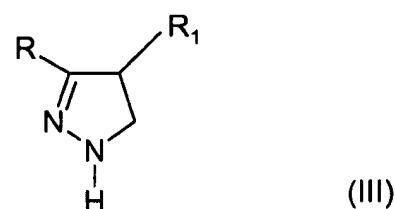
This reaction is preferably carried out in an inert organic solvent, such as for example dichloromethane.

Synthesis route A3

15

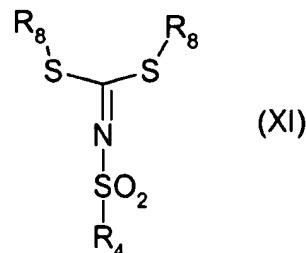
Step 1 of route A3

Reaction of a compound having formula III



20

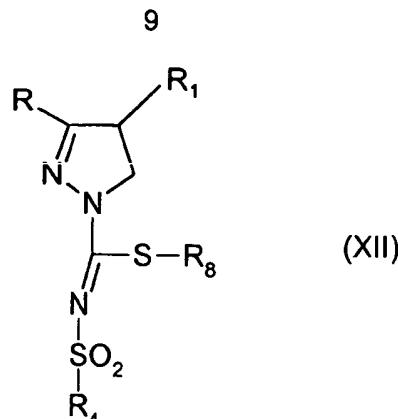
with a dithioimidocarbonic ester derivative having formula (XI) .



wherein R₈ represents a C₁₋₃ alkyl group.

25

This reaction is preferably carried out in a polar organic solvent, such as for example acetonitrile.



This reaction gives a carboximidothioic ester derivative having formula (XII).

Compounds having formula (XII) wherein R, R₁ and R₄ have the meaning as described herein above for compound (I) and wherein R₈ represents a C₁₋₃ alkyl group are new.

5

Step 2 of route A3

Reaction of a compound having formula (XII) with an amine gives a compound having formula (I).

10

This reaction is preferably carried out in a polar organic solvent, such as for example methanol.

Example I

3-(4-Chlorophenyl)-4,5-dihydro-N-((4-fluorophenyl)sulfonyl)-4-phenyl-1H-pyrazole-1-carboxamidine

15

Part A: A stirred mixture of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (5.13 gram, 20.0 mmol), 2-methyl-2-thiopseudourea hydroiodide (5.00 gram, 23.0 mmol) and pyridine (10 ml) is heated at 110 °C for 1 hour. After one night standing at room temperature diethyl ether is added and the precipitate is collected by filtration. This precipitate is washed three times with diethyl ether portions to afford a solid (9 gram). Melting point: ~230 °C. This solid is dissolved in methanol (20 ml). To the resulting solution is successively added a 2N sodium hydroxide solution (12 ml) and water (200 ml). The formed precipitate is collected by filtration, washed two times with diethyl ether and successively with diisopropyl ether. The resulting solid is dried *in vacuo* to yield 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (5.1 gram, 88 % yield). Melting point: 187-189 °C.

20

25

Part B: To a stirred mixture of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (0.50 gram, 1.68 mmol) and 4-fluorophenylsulfonyl

30

chloride (0.34 gram, 1.75 mmol) in acetonitrile (10 ml) is added N,N-dimethyl-4-aminopyridine (0.020 gram, 0.175 mmol) and triethylamine (1 ml). The resulting solution is stirred at room temperature for 30 minutes. After addition of a 2N sodium hydroxide solution and extraction with ethylacetate (400 ml), the ethylacetate layer is concentrated *in vacuo*. The resulting crude residue is further purified by means of flash chromatography (petroleum ether/diethyl ether = 1/1 (v/v), followed by ethylacetate). Subsequent concentration *in vacuo* affords solid 3-(4-chlorophenyl)-4,5-dihydro-N-((4-fluorophenyl)sulfonyl)-4-phenyl-1H-pyrazole-1-carboxamidine (0.55 gram, 72 % yield). Melting point: 214-215 °C

10

In an analogous manner the compounds having formula (I) listed below have been prepared:

4,5-Dihydro-N-((4-fluorophenyl)sulfonyl)-3-(4-methoxyphenyl)-4-(4-methoxyphenyl)-1H-pyrazole-1-carboxamidine: Melting point: 155-156 °C

15

4,5-Dihydro-3-(4-methoxyphenyl)-4-(4-methoxyphenyl)-N-((4-methoxyphenyl)sulfonyl)-1H-pyrazole-1-carboxamidine: Melting point: 148-150 °C

3-(4-Chlorophenyl)-4,5-dihydro-4-phenyl-N-((2,4,6-trimethylphenyl)sulfonyl)-1H-pyrazole-1-carboxamidine: Melting point: 221-222 °C

20

Example II

N¹,N¹-Dimethyl-N²-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine

25

Part A: A stirred mixture of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (12.0 gram, 46.8 mmol), [(4-chlorophenyl)sulfonyl]dithioimidocarbonic acid dimethyl ester (CAS: 13068-12-7) (9.20 gram, 31.1 mmol) and triethylamine (15 ml) in acetonitrile (200 ml) is heated at reflux temperature for 20 hours. An additional portion of 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (12.0 gram, 46.8 mmol) is added and the resulting mixture is heated at reflux temperature for another 16 hours. After concentration *in vacuo*, dichloromethane is added and the resulting solution is washed twice with water and dried over anhydrous Na₂SO₄. After filtration and evaporation *in vacuo* the residue is further purified by flash chromatography (diethyl ether/ petroleum ether = 1/1 (v/v)) to give 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboximidothioic acid methyl ester (12.5 gram, 80% yield based on [(4-chlorophenyl)sulfonyl]dithioimidocarbonic acid dimethyl ester) as an amorphous solid.

30

35

5 **Part B:** To a stirred mixture of 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboximidothioic acid methyl ester (4.20 gram, 8.30 mmol) in methanol (75 ml) is added dimethylamine (10 ml) and dichloromethane (75 ml) and the resulting solution is stirred at room temperature
10 for 6 hours. Evaporation *in vacuo* and subsequent flash chromatographic purification (diethyl ether/ petroleum ether = 1/1 (v/v), followed by diethyl ether) gives a solid which is further purified by recrystallisation from diisopropyl ether to yield N¹-dimethyl-N²-((4-chloro-phenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-

10 1-carboxamidine (2.63 gram, 63 % yield). Melting point: 182 °C.

In an analogous manner the compounds having formula (I) listed below have been prepared:

15 N-Methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-(3-pyridyl)-1H-pyrazole-1-carboxamidine. Melting point: 101-105 °C.

N-Methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-(4-pyridyl)-1H-pyrazole-1-carboxamidine. Melting point: 112-115 °C.

Example III

20 **N-Methyl-N'-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine**
25 **Part A:** To a solution of N-((4-chlorophenyl)sulfonyl)carbamic acid methyl ester (CAS: 34543-04-9) (2.99 gram, 12.0 mmol) and pyridine (4 ml) in 1,4-dioxane (20 ml) is added 3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole (3.39 gram, 13.2 mmol) and the resulting mixture is stirred for 4 hours at 100 °C. After concentration *in vacuo* the residue is dissolved in dichloromethane, successively washed with water, 1N HCl and water, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to a volume of 20 ml. Methyl-tert-butyl ether (60 ml) is added and the resulting solution is concentrated to a volume of 20 ml. The formed crystals are collected by filtration and recrystallised from methyl-tert-butyl ether to give 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide (4.75 gram, 76 % yield) Melting point: 211-214 °C.

35 **Part B:** A mixture of 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamide (3.67 gram, 7.75 mmol) and phosphorus pentachloride (1.69 gram, 8.14 mmol) in chlorobenzene (40 ml) is heated at reflux for 1 hour. After thorough concentration *in vacuo*, the formed N-((4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-

carboximidoyl chloride is suspended in dichloromethane and reacted with cold methylamine (1.5 ml). After stirring at room temperature for 1 hour, the mixture is concentrated *in vacuo*. The residue is crystallised from diethyl ether to give N-methyl-N'-(4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-
5 1H-pyrazole-1-carboxamidine (2.29 gram, 61 % yield). Melting point: 96-98 °C (dec.).

In an analogous manner the compounds having formula (I) listed below have been prepared:

10 N-Methyl-N'-(3-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-
1H-pyrazole-1-carboxamidine. Melting point: 156-160 °C.
N-Propyl-N'-(4-fluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-
pyrazole-1-carboxamidine. Melting point: 129-138 °C.
N-(2-Propyl)-N'-(4-fluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-
15 1H-pyrazole-1-carboxamidine. Melting point: 110-112 °C.
N-(2-Propyl)-N'-(4-chlorophenyl)sulfonyl)-3-(4-pyridyl)-4,5-dihydro-4-phenyl-1H-
pyrazole-1-carboxamidine. Melting point: Amorphous.
N¹-Ethyl-N¹-methyl-N²-(4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-
phenyl-1H-pyrazole-1-carboxamidine. Melting point: 184 °C.
20 N¹-Ethyl-N¹-methyl-N²-(4-fluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-
phenyl-1H-pyrazole-1-carboxamidine. Melting point: 173-176 °C.
N¹,N¹-Dimethyl-N²-(4-(trifluoromethyl)phenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-
dihydro-4-phenyl-1H-pyrazole-1-carboxamidine. Melting point: 195-196 °C.
N¹,N¹-Dimethyl-N²-(3-methylphenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-
25 phenyl-1H-pyrazole-1-carboxamidine. Melting point: 195-198 °C.
N¹,N¹-Dimethyl-N²-(3-methoxyphenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-
phenyl-1H-pyrazole-1-carboxamidine. Melting point: 204-206 °C.
N-Ethyl-N'-(4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-
pyrazole-1-carboxamidine. Melting point: Amorphous.
30 N-Dimethylamino-N'-(4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-
phenyl-1H-pyrazole-1-carboxamidine. Melting point: 155-159 °C.
N-Methyl-N'-(4-(trifluoromethyl)phenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-
phenyl-1H-pyrazole-1-carboxamidine. Melting point: Amorphous.
N¹,N¹-Dimethyl-N²-(2-methylphenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-
35 phenyl-1H-pyrazole-1-carboxamidine. Melting point: 148-151 °C.
N-Methyl-N'-(2,4-difluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-
phenyl-1H-pyrazole-1-carboxamidine. Melting point: 85 °C.

Example IV**(-)-(4S)-N-methyl-N'-(4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine**

5 (-)-(4S)-N-Methyl-N'-(4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-
4-phenyl-1H-pyrazole-1-carboxamidine (7.16 gram, 0.0147 mol) ($[\alpha]^{25}_D = -150^\circ$, c = 0.01, MeOH) (melting point: 169-170 °C) was obtained via chiral
chromatographic separation of racemic N-methyl-N'-(4-chlorophenyl)sulfonyl)-3-
10 (4-chlorophenyl)-4,5-dihydro-4-phenyl-1H-pyrazole-1-carboxamidine (18 gram,
0.037 mol) using a Chiralpak AD, 20 µm chiral stationary phase. The mobile
phase consisted of a mixture of hexane/ethanol (80/20 (v/v)) and 0.1 %
ammonium hydroxide (25 % aqueous solution).

15 In an analogous manner the optically pure compounds listed below have been
prepared from the corresponding racemates:

(-)-(4S)-N-Ethyl-N'-(4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-4-
phenyl-1H-pyrazole-1-carboxamidine: ($[\alpha]^{25}_D = -126^\circ$, c = 0.01, CHCl₃); Melting
point: 172-175 °C. Stationary phase: Chiralcel OD. Mobile phase: A mixture of
heptane/2-propanol (85/15 (v/v)).

20 (-)-(4S)-N-Dimethylamino-N'-(4-chlorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-
dihydro-4-phenyl-1H-pyrazole-1-carboxamidine: ($[\alpha]^{25}_D = -132^\circ$, c = 0.01, CHCl₃);
Melting point: 218-224 °C. Stationary phase: Chiralcel OD. Mobile phase: A
mixture of heptane/2-propanol (85/15 (v/v)).

25 (-)-(4S)-N-Methyl-N'-(4-(trifluoromethyl)phenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-
dihydro-4-phenyl-1H-pyrazole-1-carboxamidine: ($[\alpha]^{25}_D = -131^\circ$, c = 0.01, CHCl₃);
Melting point: 157-160 °C. Stationary phase: Chiralcel OD. Mobile phase: A
mixture of heptane/2-propanol (85/15 (v/v)).

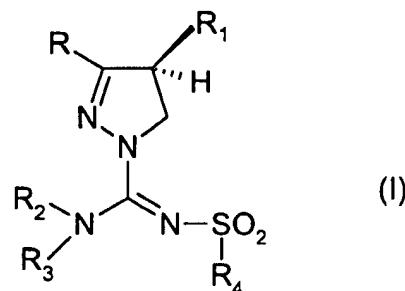
30 (-)-(4S)-N¹,N¹-Dimethyl-N²-(2-methylphenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-
dihydro-4-phenyl-1H-pyrazole-1-carboxamidine: ($[\alpha]^{25}_D = -88^\circ$, c = 0.01, MeOH);
Melting point: Amorphous. Stationary phase: Chiralpak AD. Mobile phase:
Ethanol.

(-)-(4S)-N-Methyl-N'-(2,4-difluorophenyl)sulfonyl)-3-(4-chlorophenyl)-4,5-dihydro-
4-phenyl-1H-pyrazole-1-carboxamidine: ($[\alpha]^{25}_D = -129^\circ$, c = 0.01, MeOH); Melting
point: Amorphous. Chiralpak AD. Mobile phase: Methanol.

Claims

1. The enantiomer having S configuration at the 4-position of their 4,5-dihydro pyrazole ring of a compound of formula (I)

5



wherein

- R and R₁ are the same or different and represent 3-pyridyl or 4-pyridyl, or phenyl which may be substituted with halogen or methoxy,
- R₂ and R₃ are the same or different and represent hydrogen, alkyl (1-3 C) or dimethylamino
- R₄ represents phenyl which may be substituted with 1, 2 or 3 substituents selected from the group halogen atoms, trifluoromethyl, methoxy and alkyl (1-3 C)

and tautomers, prodrugs and salts thereof.

10 2. A compound having formula (I) as claimed in claim 1, wherein R is the group 4-chlorophenyl, R₁ is phenyl, R₂ is hydrogen, R₃ is methyl and R₄ represents 4-chlorophenyl, and salts thereof.

15 3. A pharmaceutical composition containing at least one compound as claimed in claim 1 as an active component.

20 4. A method of preparing pharmaceutical compositions characterized in that a compound as claimed in claim 1 is brought in a form suitable for administration.

25 5. Process for the preparation of compounds having formula I, characterized in that the racemic mixture of a compound having formula I is separated into the levorotatory and the dextrorotatory enantiomers.

30

6. A method of treating psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders and appetite disorders, obesity, neurological disorders such as Parkinson's disease, dementia, 5 distonia, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, ischaemia, pain and other CNS-diseases involving cannabinoid neurotransmission, characterized in that a compound as claimed in claim 1 is used.
- 10 7. A method of treating gastrointestinal disorders involving cannabinoid neurotransmission, characterized in that a compound as claimed in claim 1 is used.
- 15 8. A method of treating cardiovascular disorders involving cannabinoid neurotransmission, characterized in that a compound as claimed in claim 1 is used.

INTERNATIONAL SEARCH REPORT

Interr. Application No.

PCT/EP 02/03079

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07D231/06 C07D401/04 A61K31/415 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PERTWEE, R. G.: "Pharmacology of Cannabinoid Receptor Ligands" CURRENT MED. CHEM., vol. 6, 1999, pages 635-664, XP000923352 cited in the application Pages 657-659, chapter "Diarylpyrazoles"; and page 641, figure 5. ---	1-5
A	US 5 624 941 A (BARTH, F. ET AL.) 29 April 1997 (1997-04-29) Claim 1, formula (I); column 26, lines 27-65; column 28, lines 41-59. ---	1-5
A	US 4 070 365 A (VAN DAALEN, J. J. ET AL.) 24 January 1978 (1978-01-24) Claim 1; abstract. ---	1-5 -/-



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

18 June 2002

Date of mailing of the international search report

25/06/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Weisbrod, T

INTERNATIONAL SEARCH REPORT

Internat'l Application No
PCT/EP 02/03079

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 173 323 A (BAYER AG) 5 March 1986 (1986-03-05) Abstract; claim 1; page 32, example 1. -----	1-5

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr. ref Application No

PCT/EP 02/03079

Patent document cited in search report		Publication date	Patent family member(s)	Publication date	
US 5624941	A	29-04-1997	FR 2692575 A1 FR 2713224 A1 FR 2713225 A1 AT 149489 T AU 4143893 A BR 1100409 A3 BR 9302435 A CA 2098944 A1 CZ 9301172 A3 DE 69308395 D1 DK 576357 T3 EP 0576357 A1 ES 2101258 T3 FI 932891 A GR 3023535 T3 HU 64526 A2 IL 106099 A JP 3238801 B2 JP 6073014 A MX 9303664 A1 NO 932296 A NZ 247961 A RU 2119917 C1 SK 65493 A3 ZA 9304511 A AT 154012 T AU 685518 B2 AU 7899994 A BR 1100984 A3 CA 2136893 A1 CN 1110968 A ,B CZ 9403016 A3 DE 69403614 D1 DE 69403614 T2 DK 656354 T3 EP 0656354 A1 ES 2105575 T3 FI 945690 A GR 3024470 T3 HK 1000599 A1 HU 71498 A2 IL 111719 A JP 3137222 B2 JP 7309841 A JP 2001026541 A NO 944625 A NZ 270025 A PL 306067 A1 RU 2141479 C1 SG 68570 A1	24-12-1993 09-06-1995 09-06-1995 15-03-1997 06-01-1994 13-10-1999 11-01-1994 24-12-1993 16-03-1994 10-04-1997 15-09-1997 29-12-1993 01-07-1997 24-12-1993 29-08-1997 28-01-1994 15-07-1998 17-12-2001 15-03-1994 31-01-1994 27-12-1993 28-08-1995 10-10-1998 02-02-1994 22-02-1994 15-06-1997 22-01-1998 15-06-1995 14-03-2000 21-06-1995 01-11-1995 14-06-1995 10-07-1997 22-01-1998 29-12-1997 07-06-1995 16-10-1997 03-06-1995 28-11-1997 09-04-1998 28-11-1995 28-10-1999 19-02-2001 28-11-1995 30-01-2001 06-06-1995 26-09-1995 12-06-1995 20-11-1999 20-06-2000	24-12-1993 09-06-1995 09-06-1995 15-03-1997 06-01-1994 13-10-1999 11-01-1994 24-12-1993 16-03-1994 10-04-1997 15-09-1997 29-12-1993 01-07-1997 24-12-1993 29-08-1997 28-01-1994 15-07-1998 17-12-2001 15-03-1994 31-01-1994 27-12-1993 28-08-1995 10-10-1998 02-02-1994 22-02-1994 15-06-1997 22-01-1998 15-06-1995 14-03-2000 21-06-1995 01-11-1995 14-06-1995 10-07-1997 22-01-1998 29-12-1997 07-06-1995 16-10-1997 03-06-1995 28-11-1997 09-04-1998 28-11-1995 28-10-1999 19-02-2001 28-11-1995 30-01-2001 06-06-1995 26-09-1995 12-06-1995 20-11-1999 20-06-2000
US 4070365	A	24-01-1978	NL 7409433 A AR 223449 A1 AT 359775 B AT 508277 A AT 342585 B AT 529175 A AU 501280 B2	14-01-1976 31-08-1981 25-11-1980 15-04-1980 10-04-1978 15-08-1977 14-06-1979	

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Application No

PCT/EP 02/03079

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4070365	A	AU 8285075 A	13-01-1977
		BE 831232 A1	12-01-1976
		BR 7504413 A	06-07-1976
		CA 1075242 A1	08-04-1980
		CH 624675 A5	14-08-1981
		CS 188962 B2	30-03-1979
		DD 122775 A5	05-11-1976
		DE 2529689 A1	29-01-1976
		DK 310975 A ,B,	13-01-1976
		EG 11880 A	30-09-1978
		ES 439292 A1	16-02-1977
		FR 2277827 A1	06-02-1976
		GB 1514285 A	14-06-1978
		HU 178320 B	28-04-1982
		IE 41836 B1	09-04-1980
		IL 47676 A	31-01-1979
		IT 1044358 B	20-03-1980
		JP 1368569 C	11-03-1987
		JP 51041358 A	07-04-1976
		JP 61023162 B	04-06-1986
		OA 5057 A	31-12-1980
		PL 193676 A1	17-07-1978
		SE 419644 B	17-08-1981
		SE 7507868 A	13-01-1976
		US 4156007 A	22-05-1979
		YU 176475 A1	30-06-1982
		ZA 7504203 A	23-02-1977
EP 0173323	A 05-03-1986	DE 3431926 A1	06-03-1986
		AU 4665285 A	06-03-1986
		BR 8504157 A	24-06-1986
		CA 1218366 A1	24-02-1987
		DD 237782 A5	30-07-1986
		DK 392985 A	01-03-1986
		EP 0173323 A1	05-03-1986
		ES 546559 D0	01-03-1986
		ES 8604942 A1	01-08-1986
		GR 852092 A1	30-12-1985
		HU 41210 A2	28-04-1987
		JP 61060684 A	28-03-1986
		ZA 8506593 A	30-04-1986